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Environmental Styrene Exposure and Sensory and Motor Function in Gulf Coast Residents

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Background: Although styrene is an established neurotoxicant at occupational exposure levels, its neurotoxicity has not been characterized in relation to general population exposures. Further, occupational research to date has focused on central nervous system impairment.

Objective: We assessed styrene-associated differences in sensory and motor function among Gulf coast residents.

Methods: We used 2011 National Air Toxics Assessment estimates of ambient styrene to determine exposure levels for 2,956 nondiabetic Gulf state residents enrolled in the Gulf Long-term Follow-up Study, and additionally measured blood styrene concentration in a subset of participants 1 to 2 y after enrollment ($n = 310$). Participants completed an enrollment telephone interview and a comprehensive test battery to assess sensory and motor function during a clinical follow-up exam 2 to 4 y later. Detailed covariate information was ascertained at enrollment via telephone interview. We used multivariate linear regression to estimate continuous differences in sensory and motor function, and log-binomial regression to estimate prevalence ratios for dichotomous outcomes. We estimated associations of both ambient and blood styrene exposures with sensory and motor function, independently for five unique tests.

Results: Those participants in the highest 25% vs. lowest 75% of ambient exposure and those in the highest 10% vs. lowest 90% of blood styrene had slightly diminished visual contrast sensitivity. Mean vibrotactile thresholds were lower among those in the highest vs. lowest quartile of ambient styrene and the highest 10% vs. lowest 90% of blood styrene (−0.13 log microns; 95% CI: −0.23, −0.03 and −0.39 log microns; 95% CI: −0.72, −0.05, respectively). The highest vs. lowest quartile of ambient styrene was associated with significantly poorer postural stability, and (unexpectedly) with significantly greater grip strength.

Discussion: We observed associations between higher styrene exposure and poorer visual, sensory, and vestibular function, though we did not detect associations with reduced voluntary motor system performance. Associations were more consistent for ambient exposures, but we also found notable associations with measured blood styrene. https://doi.org/10.1289/EHP3954

Introduction

Styrene [also known as ethenylbenzene, chemical formula C_8H_8 (or, more precisely, $C_6H_5CH=CH_2$), Chemical Abstract Service (CAS) number 100-42-5] is a hydrocarbon used in plastics, fiberglass, rubber, and resins. It is used to manufacture products such as insulation, fiberglass boats, automotive parts, car tires, Styrofoam, and plastic drinking glasses (ATSDR 2010). After the disposal of styrene-based products, styrene is released primarily into air, though smaller amounts are detected in soil and water (ATSDR 2012). Ambient styrene, a volatile organic compound, breaks down in the atmosphere within 1 to 2 d (ATSDR 2010).

The general population is exposed to styrene primarily through inhalation of tobacco smoke, off-gassing of building materials, and vehicle and industrial emissions (ATSDR 2011; U.S. EPA 1994). The principal route of styrene exposure is through inhalation of contaminated air (ATSDR 2010). Typically, indoor air contains higher styrene levels than outdoor air (Wallace 1986) due to emissions from building materials, consumer products, and tobacco smoke (CDC 2009). Emissions from industrial activities and motor vehicle exhaust are the primary sources of styrene in outdoor air.

The half-life of styrene in blood is approximately 13 h, so blood styrene levels reflect recent exposure. Approximately 40% of the U.S. adult population has measurable levels of styrene in their blood (Bonanno et al. 2001; CDC 2009).

Although the occupational styrene literature has focused on central nervous system toxicity (ATSDR 2010), the peripheral nervous system may be another critical target for styrene's neurotoxic effects, particularly at environmental levels. The peripheral nervous system is composed of multiple nerve fiber populations, including long, large-diameter, heavily myelinated neurons with limited tolerance to physiological and toxicological insult. Therefore, portions of the peripheral nervous system may be more vulnerable to small perturbations, resulting in impaired peripheral nerve performance earlier, and at lower exposure levels, than are other neurologic tissues.

Low-level, chronic styrene exposure may affect neurologic function at environmental levels relevant to the general population (Cohen et al. 2002). The Gulf States are home to over half of all U.S. styrene production (ATSDR 2010; NTP 2014), as well as to many industrial and manufacturing facilities that use and emit styrene in the production of plastics, rubber, and fiberglass. This geographic clustering of industries potentially exposes Gulf residents to disproportionately high environmental styrene emissions from petrochemical, manufacturing, and coastal fishing and boating operations (Helper et al. 2012). We investigated associations between environmental styrene exposure, assessed as both blood and air concentrations, and sensory and motor function.

Methods

Study Design and Participants

The Gulf Long-term Follow-up Study (GuLF STUDY) is a prospective cohort of adults (age 21 and older) who participated in

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oil spill response activities and others who received safety training but were not hired, following the *Deepwater Horizon* disaster (Engel et al. 2017; Kwok et al. 2017). Participants enrolled in the GuLF STUDY between March 2011 and March 2013 ($N = 32{,}608$). All GuLF STUDY cohort participants living in the Gulf region who spoke English or Spanish were invited to participate in a home visit. Ultimately, 11,193 home visits were completed between May 2011 and May 2013. A subset of home visit participants ($n = 1{,}055$) enrolled in a Chemical Biomonitoring Study (CBS) between May 2012 and July 2013 (Werder et al. 2017). The CBS initially oversampled for nonsmokers, women, and *Deepwater Horizon* clean-up workers. To reach the target sample size before the end of the home visit period of the GuLF STUDY, recruitment efforts were later expanded to include all home visit participants. Participation in the CBS involved providing an extra blood sample for measuring styrene and other compounds and completing a questionnaire about usual and recent exposures and relevant activities. Because styrene is rapidly cleared from the body and blood measurements were obtained 2 to 3 y after the oil spill, these levels represent usual, ongoing exposures (i.e., they are not due to oil spill cleanup work).

A subset of GuLF STUDY participants ($n = 3{,}403$) residing within approximately 60 miles of study clinics in New Orleans, Louisiana, and Mobile, Alabama, were recruited for a follow-up clinical examination between August 2014 and July 2016. Participation involved completing a clinical examination in one of the two clinics. Examinations included anthropometric measurements, biological sample collection, standardized computer-assisted neurocognitive testing, sensory and motor function evaluations, pulmonary function testing, and interviews on mental health and other factors.

Of the 3,403 participants who completed the follow-up clinical exam, 3,329 (98%) reported addresses at enrollment that were successfully geocoded to a 2010 U.S. Census Bureau census tract. From this sample of participants with known residential locations, we excluded anyone with missing outcome information for all five sensory and motor function tests ($n = 8$), missing demographic information ($n = 37$), or missing covariate information ($n = 22$). Of the remaining 3,262 participants with complete exposure, outcome, and covariate information, we restricted analyses to participants with no self-reported physician diagnosis of diabetes (i.e., we excluded 303 diabetics and 3 participants missing diagnosis information) because neuropathy is a known complication of diabetes (Freeman 2014). These exclusions resulted in a final analytic sample of 2,956.

A total of 348 CBS participants with blood samples sufficient for quantification of styrene concentration also participated in the follow-up clinical examination. Of those participants, we excluded five participants missing all sensory and motor function information. The remaining 343 participants had complete exposure, outcome, demographic, and covariate information. We then excluded known diabetics ($n = 33$), for a final analytic sample of 310.

Participants provided written informed consent and the Institutional Review Board of the National Institute of Environmental Health Sciences approved this study.

National Air Toxics Assessment (NATA)

The United States Environmental Protection Agency (EPA) 2011 National Air Toxics Assessment (NATA) (U.S. EPA 2016) estimates annual average ambient air toxic concentrations for each U.S. Census tract. NATA evaluates 180 air toxics across the United States using emissions inventories; dispersion, photochemical, and exposure modeling; and toxicity analyses. We used NATA styrene estimates to indicate typical long-term environmental exposure by geocoding self-reported home addresses at enrollment, mapping each participant's location, and matching them to a corresponding 2010 U.S. Census tract. The 2011 NATA annual average ambient styrene concentration ($\mu g/m^3$) corresponding to an individual's home census tract was applied as the estimate of usual ambient styrene exposure.

Blood Styrene Measurement

We collected 10 mL of blood for styrene measurement using tubes containing potassium oxalate and sodium fluoride anticoagulant; tubes and stoppers were pretreated by the Centers for Disease Control and Prevention (CDC) laboratory to remove volatile organic compounds (VOCs) to minimize precollection contamination (Chambers et al. 2005; Chambers et al. 2008). Samples were stored at 4°C until being shipped overnight on cold packs in biweekly batches to the Division of Laboratory Sciences, National Center for Environmental Health, CDC, in Atlanta, Georgia, for analysis of VOCs. Styrene was analyzed using equilibrium headspace solid-phase microextraction with benchtop gas chromatography/mass spectrometry following standard CDC procedures (Blount et al. 2006; Chambers et al. 2006).

Sensory and Motor Function Testing

The sensory and motor function testing battery, which was used in an earlier study of chronic, low-level neurotoxicants (Starks et al. 2012), included tests of visual acuity, visual contrast sensitivity, handgrip strength, vibrotactile threshold, standing steadiness, and single leg stance. These tests evaluate sensory and motor functions corresponding to neurotoxic effects that have been demonstrated in association with occupational solvent exposure (Campagna et al. 1995; Letz et al. 1994).

Visual acuity, an indicator of visual sharpness or clarity, was assessed binocularly (in both eyes simultaneously) using a standard vision testing instrument, the Optec 1,000 (Optec, Inc.). Results from this test were used to determine eligibility for analyses of visual contrast sensitivity. Participants with binocular visual acuity scores of 20/50 or worse were excluded from visual contrast sensitivity analyses.

Visual contrast sensitivity was evaluated with the Optec 1,000 Functional Assessment of Contrast Sensitivity test. Circular stimuli consisting of alternating light and dark bars were presented. Nine stimuli of decreasing contrast were presented at each of 5 spatial frequencies (1.5, 3, 6, 12, and 18 cycles per degree). The weakest contrast correctly identified was recorded for each spatial frequency. Results are presented as mean differences in contrast scores because we did not have access to the information required to present units of luminance contrast.

Standing steadiness was evaluated with the Advanced Mechanical Technology, Inc. force platform (AMTI). Participants were instructed to stand on the platform without moving. Standing steadiness was measured twice with participant eyes open and twice with participant eyes closed. The force platform and associated software capture and store the forces applied to the platform by the participant's feet during each trial. The force signals are processed and plotted as a time series of locations (path) of the participant's center of pressure. The mean sway speeds in millimeters per second obtained during the two eyes open and the two eyes closed trials were used for statistical analysis of standing steadiness.

Single leg stance was evaluated by asking the participant to stand on one leg and maintain upright balance for 30 s (Tyson and Connell 2009). If the participant was unable to maintain their upright balance for the entire 30-s test interval, then the procedure was repeated up to two additional times. Inability to maintain single leg balance was defined as a need for steadying by the examiner to prevent falling or participant inability to comply

with instructions to stand on only one leg for the entire 30-s test interval (i.e., the participant placed the other foot on the ground to prevent falling). Examiners indicated whether, and on which attempt, the participant was able to maintain his or her balance for the entire 30-s test interval. We modeled the outcome for single leg stance as inability to maintain upright balance for 30 s.

Vibrotactile sensory acuity was evaluated using a portable Vibratron II electromechanical vibrometer at a frequency of 120 Hz (Physitemp, Inc.). Calibration of all vibrometer devices was conducted using a single NIST-traceable piezoelectric accelerometer (Model SEN021F, PCB Piezotronics). The vibrometer devices are internally adjustable and were calibrated so that each produced known and equal vibration amplitudes at specific values over the full range of displayed "vibration units." Examiners manually controlled the delivered vibration amplitude, obtaining five vibration threshold values (three descending and two ascending values) for each great toe (ventral surface). After discarding the first value, the final vibrotactile threshold for each toe was the median obtained from the remaining four values, which was converted to log microns of peak-to-peak amplitude displacement for statistical analysis.

Handgrip strength was assessed with a baseline digital hydraulic hand dynamometer that records the maximum force exerted by the participant's whole-hand grip. Using standard hand and arm positions, participants performed three grip strength measures for each hand (Mathiowetz et al. 1984). We used the bilateral mean of all six tests, measured in pounds, as the summary metric in statistical analyses.

Statistical Analysis

We used multivariate linear regression to estimate continuous differences in sensory and motor function per unit change in the exposure metrics (ambient styrene, βa and blood styrene, βb). For ease of interpretation, higher values indicate better performance for all continuous outcomes (mean contrast sensitivity score, vibrotactile threshold, handgrip strength, and postural sway speed). To achieve this internal consistency, we multiplied the raw values for vibrotactile threshold and postural sway speed by negative one. For tests of contrast sensitivity, we compared styrene-exposed with unexposed participants and evaluated differences in adjusted mean scores (adjustment covariates reported below) between exposure groups at each spatial frequency. We used log-binomial regression to estimate prevalence ratios (ambient, PRa and blood, PRb) and corresponding 95% confidence intervals (95% CI) for single leg stance. PRs above 1 indicate poorer test performance (i.e., inability to maintain balance for the full 30 s), and PRs below 1 indicate better test performance.

We analyzed each exposure type (i.e., NATA-estimated ambient styrene concentration and measured blood styrene concentration) separately using identical statistical methods for both. For associations with ambient styrene ($N = 2{,}956$), apart from visual contrast sensitivity, concentrations were categorized in quartiles, with the lowest quartile ($\leq 0.01\ \mu g/m^3$) designated as the referent group. For visual contrast sensitivity, we compared the highest quartile with the lower three quartiles combined. In addition to estimating associations with quartiles of ambient exposure, we evaluated exposure–response relationships using Wald tests of linear trend in adjusted models. For trends tests, we modeled exposure as an ordinal variable with integer scores for each quartile and reported corresponding *p*-values (*p*-trend).

For analyses of measured blood styrene ($n = 310$), exposure was dichotomized at the 90th percentile of the distribution, defining the top decile of blood measurements (0.83–3.03 ng/mL) as exposed and the remaining 90% as 'unexposed' ($0.011 - < 0.83$ ng/mL). For all tests, we additionally modeled blood styrene as the top quartile ("exposed," ≥ 0.19 ng/mL) in comparison with the three lower quartiles ("unexposed," $0.011 - < 0.19$ ng/mL). We used all measured blood styrene values, including the actual values below the limit of detection (LOD = 0.03 ng/mL) (Whitcomb and Schisterman 2008).

All models were adjusted for gender (female vs. male), age (continuous years), race (white, black, other), education (less than high school or equivalent, high school or general equivalency diploma, some college or two-year degree, four-year college graduate or more), employment status (self-reported currently working vs. currently not working), alcohol consumption (any drinks in the past 12 months vs no drinks in the past 12 months), and smoking status (current vs. former or never). Participants were asked to report which racial category they considered themselves to be members of, choosing from: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, or Other. Based on the distribution of responses and heterogeneity among specified "other" responses, we categorized participants as white, black, or other. Because participants identifying as Hispanic represented only 2% of the study population for both ambient and blood styrene analyses, we did not define race with regard to ethnicity, instead adjusting for race only. Covariate information was obtained during the enrollment interview, and adjustment covariates were selected based on relations among different variables and a directed acyclic graph (DAG) (Greenland et al. 1999) of the theoretical relationship between styrene exposure and sensory and motor function (Figure S2). For analyses of vibrotactile threshold and handgrip strength, we additionally adjusted for height. For visual contrast sensitivity, we restricted analyses to participants with better than 20/50 visual acuity and additionally adjusted for use of vision correction (i.e., wearing glasses or corrective lenses). Owing to concerns about overwhelming population variance in the handgrip strength tests, we also examined the influence of weight and gender on these associations.

In sensitivity analyses, we adjusted models for participation in the *Deepwater Horizon* oil spill response or cleanup (≥1 day vs. none) to account for potential fundamental differences between cleanup workers and nonworkers. We assessed effect measure modification using analyses stratified by age (≤45 y vs. >45 y), sex (male vs. female), race (white, black, other), employment status (working vs. not working), and residential location (urban vs. rural). Interaction *p*-values (*p*-interaction) were derived from multivariate analysis of variance using *F*-tests of the overall interaction between quartiles of ambient styrene and the modifier of interest. Due to sample size limitations, we conducted interaction analyses for ambient exposures only.

Because eligibility criteria required that participants completed at least one sensory or motor function test from the full battery (but not all such tests), analytic sample sizes vary between tests.

All statistical analyses were conducted in SAS (version 9.4; SAS Institute Inc).

Results

CBS participants, all of whom were also in the ambient analysis, were largely similar to those in the larger study with respect to demographic characteristics (Table 1). Approximately 70% of participants completed their examinations at the Alabama testing site, less than half attended college, three-fourths were male, and about half were younger than age 45 y. Half of all participants were white, and about 40% were black. The "other" race group identified as Asian (7%), multiracial (38%), or various other responses (55%) (data not shown). Among CBS participants, 85% completed all five sensory and motor function tests, in

Table 1. Demographic characteristics ascertained at enrollment according to estimated ambient styrene exposures in participants living in the Gulf states ($N = 2,956$) and blood styrene concentrations among Chemical Biomonitoring Study (CBS) participants ($n = 310$).

	Estimated ambient styrene quartiles (%) ($N = 2,956$)					Blood styrene (%) ($n = 310$)				
Characteristic	*N* (%)	Q1	Q2	Q3	Q4	*N* (%)	Q1–Q3	Q4	≤90th	>90th
Clinical site[a]										
Louisiana	904 (31)	52	43	22	5	87 (28)	29	26	29	23
Alabama	2,052 (69)	48	57	78	95	223 (72)	71	74	71	77
Age, years										
<30	463 (16)	13	14	16	19	59 (19)	18	21	18	26
30–45	1,022 (35)	29	31	36	41	110 (36)	37	31	35	35
>45	1,471 (50)	57	55	47	39	141 (46)	45	48	46	39
Race[b]										
White	1,520 (51)	72	58	49	26	156 (50)	51	48	51	42
Black	1,180 (40)	13	35	43	69	131 (42)	42	43	42	48
Other	256 (9)	15	7	8	5	23 (7)	7	9	7	10
Sex										
Female	689 (23)	21	23	23	26	77 (25)	24	27	24	35
Male	2,267 (77)	79	77	77	74	233 (75)	76	73	76	65
Body Mass Index, kg/m^2										
≤Normal (<25)	782 (27)	29	27	24	26	87 (28)	25	36	28	32
Overweight (25 − < 30)	1,131 (38)	38	40	40	36	121 (39)	40	36	39	39
Obese (≥30)	1,043 (35)	34	33	36	39	102 (33)	35	27	33	29
Education										
<High school	625 (21)	26	20	17	22	66 (21)	21	21	22	16
High school graduate	1,037 (35)	35	30	36	39	116 (37)	36	42	37	42
Some college	873 (30)	26	33	30	29	92 (30)	29	31	29	35
≥College graduate	421 (14)	13	17	17	10	36 (12)	13	6	12	6
Work status[c]										
Employed	1,559 (53)	57	53	52	49	165 (53)	53	53	54	48
Unemployed	1,397 (47)	43	47	48	51	145 (47)	47	47	46	52
Current drinker										
Yes	2,132 (72)	71	74	75	69	215 (69)	68	73	68	84
No	824 (28)	29	26	25	31	95 (31)	32	27	32	16
Current smoker										
Yes	1,009 (34)	33	36	34	34	79 (26)	22	36	24	35
No	1,947 (66)	67	64	66	66	231 (75)	78	64	76	65
Oil spill response work[d]										
≥1 day	2,518 (85)	84	87	84	86	275 (89)	88	91	89	90
None	438 (15)	16	13	16	14	35 (11)	12	9	11	10
Vision correction[e]										
Yes	1,220 (43)	45	43	41	41	133 (44)	42	52	44	52
No	1,647 (57)	55	57	59	59	166 (56)	58	48	56	48
Missing (N)	*89*	*21*	*27*	*24*	*17*	*11*	*8*	*2*	*11*	*0*
Poor vision[e]										
Yes	538 (19)	21	15	20	18	65 (22)	20	27	21	26
No	2,335 (81)	79	85	80	82	235 (78)	80	73	79	74
Missing (N)	*83*	*21*	*25*	*23*	*14*	*10*	*8*	*2*	*10*	*0*

Note: Enrollment occurred from March 2011 until March 2013.
[a]Clinical exams took place at two sites: Louisiana State University in New Orleans, Louisiana and the University of Southern Alabama in Mobile, Alabama.
[b]Participants were asked to report which racial category they considered themselves to be, choosing from: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White, or Other. Based on the distribution of responses and heterogeneity among specified 'other' responses, we categorized participants as white, black, or other.
[c]Work status at enrollment: Employed, reported working; Unemployed, reported unemployed, looking for work, laid off, on leave, retired, unable to work, keeping house, student, other.
[d]Oil spill response work includes all tasks. Participants who completed safety training, but never worked on oil spill response/cleanup are classified as 'None'; participants who participated in any response work of any kind are classified as "≥1 day."
[e]Vision correction includes wearing corrective glasses and contact lenses; poor vision is definied as binocular visual acuity score 20/50 or worse; information related to vision correction and quality was only used in analyses of contrast sensitivity ($n_{ambient} = 2,250$; $n_{CBS} = 231$). Participants missing information for vision correction and/or quality were not eligible for contrast sensitivity analyses.

comparison with 81% of participants in ambient analyses. We provide descriptive statistics on sensory and motor function in this population, presented as mean outcomes by exposure status and demographic group in Tables S1 and S2, respectively. Although associations between styrene exposure and unadjusted sensory and motor performance were not obvious (Table S1), white participants and those younger than 45 years of age tended to perform better on sensory and motor function tests in comparison with the older, nonwhite counterparts (Table S2).

Because the CBS is a subpopulation completely nested within the ambient exposure population, all participants providing blood styrene measures also had ambient exposure estimates. Among CBS participants, blood and ambient styrene levels lacked concordance (Spearman correlation coefficient for ambient and blood styrene, quartiles: $\rho = 0.09$, p-value $= 0.11$; continuous: $\rho = 0.08$, p-value $= 0.18$). We observed similar results for continuous styrene within clinical sites (Louisiana: $\rho = 0.11$, p-value $= 0.33$; Alabama: $\rho = -0.07$, p-value $= 0.28$) and when stratifying by smoking status (nonsmokers: $\rho = -0.04$, p-value $= 0.52$; smokers: $\rho = 0.16$, p-value $= 0.17$), race (white: $\rho = -0.04$, p-value $= 0.66$; nonwhite: $\rho = 0.04$, p-value $= 0.64$), and age (<30 years: $\rho = -0.15$, p-value $= 0.29$; 30–45 y: $\rho = -0.11$, p-value $= 0.25$, >45 years: $\rho = 0.12$, p-value $= 0.16$). To explore the relationship between ambient and blood styrene further, we dichotomized both metrics (air and blood styrene) at their respective medians. We found that 90 individuals have ambient and blood styrene

above the median and 78 individuals have both metrics below the median, which amounts to 54% of the CBS population.

Study end points measure different neurological functionality or domains, but they do have some collinearity. The highest correlations are between vibrotactile threshold and postural stability (Spearman correlation coefficient, $\rho = 0.44$; p-value < 0.0001), vibrotactile threshold and single leg stance ($\rho = 0.23$; p-value < 0.0001), and postural stability and single leg stance ($\rho = 0.23$; p-value < 0.0001). Grip strength and contrast sensitivity are less correlated with the other tests. The range of Spearman correlation coefficients is -0.18 (for contrast sensitivity and vibrotactile threshold, p-value < 0.0001) to 0.44 (data not shown).

For ambient exposure analyses, we modeled associations for each quartile of styrene exposure in comparison with the lowest quartile ($\leq 0.01\ \mu g/m^3$). Styrene concentrations in the highest quartile ranged from 0.03 to $0.27\ \mu g/m^3$, with 95% of all measurements below $0.05\ \mu g/m^3$ (Figure 1). For analyses of blood styrene, we used two distinct binary exposures: one divided at the 90th percentile, 0.83 ng/mL, and one divided at the 75th percentile, 0.19 ng/mL. The maximum observed concentration was 3.03 ng/mL, with 95% of participants having blood levels below 1.36 ng/mL. 24% ($n = 70$) of participants had styrene measurements below the LOD (0.03 ng/mL). The blood exposure distribution demonstrated a pronounced right skew.

For tests of visual contrast sensitivity, we compared the highest quartile of ambient styrene with the lower three quartiles ($n = 2{,}250$). Low exposure group participants performed better than those with high exposure at each spatial frequency, with a significant difference ($p = 0.02$) at 1.5 cycles/degree (Table 2). We observed similar results for blood styrene above vs. below the 90th percentile ($n = 231$), though the smaller sample size reduced precision and the only statistically significant difference was observed at 12 cycles/degree ($p = 0.02$). These associations demonstrate a subtle, but consistent, decrement in visual contrast sensitivity associated with styrene exposure across spatial frequencies.

Increasing ambient styrene concentration was associated with reduced vibrotactile sensitivity ($n = 2{,}888$) (Figure 2). We observed a monotonic exposure–response relationship (p-trend $= 0.003$), with a significant association in the highest quartile of ambient exposure compared to the lowest quartile ($\beta a_{Q4vsQ1} = -0.13$ log microns; 95% CI: -0.23, -0.03) (Table S3). For blood styrene ($n = 307$), we observed a nonsignificant association between the highest quartile of exposure (in comparison with all others) and reduced vibrotactile sensitivity ($\beta b_{P75} = -0.19$ log microns; 95% CI: -0.42, 0.05; $p = 0.12$). When comparing the top 10% to the lower 90% of blood styrene concentrations, this association was stronger ($\beta b_{P90} = -0.39$ log microns; 95% CI: -0.72, -0.05; $p = 0.02$) (Figure 2, Table S3).

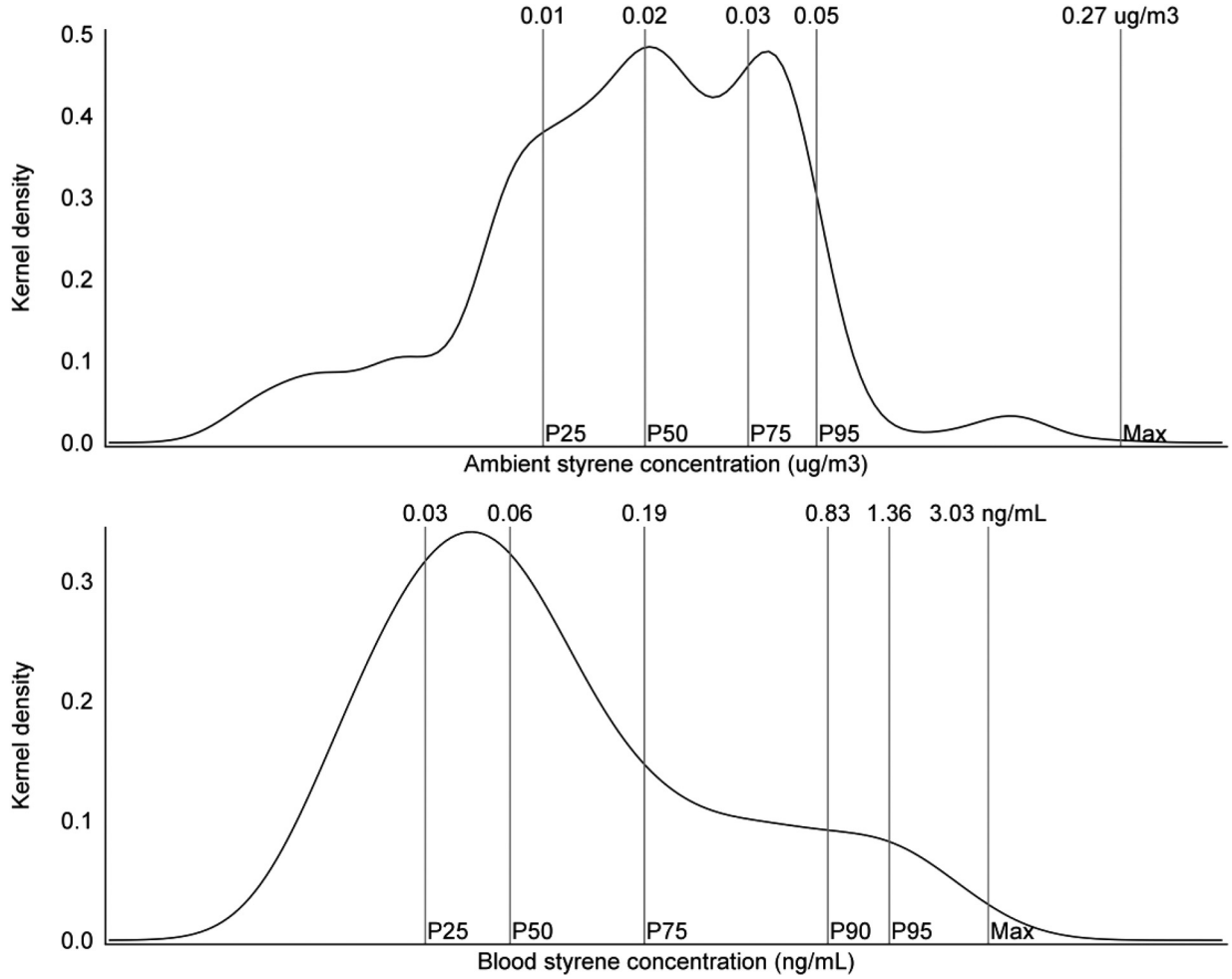

Figure 1. Probability density of styrene concentrations in air ($N = 2{,}956$) and blood ($n = 310$). Note: Ambient styrene exposure is 2011 National Air Toxics Assessment (NATA) modeled estimates of annual average concentrations (μg/m3) at the census-tract level. Blood styrene concentrations (ng/mL) are measured from a single blood draw obtained in the participant's home; limit of detection = 0.03 ng/mL. Values at the top of reference lines indicate exposure concentrations; labels at the bottom of reference lines indicate locations in the exposure distribution: P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; P90, 90th percentile; P95, 95th percentile. Max, maximum value.

Table 2. Ambient ($n = 2{,}250$) and blood ($n = 231$) styrene concentrations and differences in visual contrast sensitivity performance.

	Ambient, Q4 vs. Q1–Q3		Blood, Q4 vs. Q1–Q3		Blood, Top 10% vs. Lower 90%	
Range	Mean difference (95% CI)	*p*-Value	Mean difference (95% CI)	*p*-Value	Mean difference (95% CI)	*p*-Value
1.5	0.11 (0.02, 0.21)	0.02	0.14 (−0.14, 0.42)	0.33	0.12 (−0.29, 0.52)	0.58
3	0.10 (−0.001, 0.19)	0.05	0.26 (−0.05, 0.56)	0.10	0.31 (−0.14, 0.75)	0.17
6	0.02 (−0.13, 0.16)	0.83	−0.16 (−0.58, 0.25)	0.44	0.36 (−0.25, 0.96)	0.25
12	0.14 (−0.01, 0.30)	0.07	0.28 (−0.21, 0.77)	0.26	0.82 (0.11, 1.52)	0.02
18	0.09 (−0.06, 0.24)	0.22	0.05 (−0.39, 0.49)	0.81	0.60 (−0.03, 1.24)	0.06

Note: Models adjusted for vision correction, gender, age, race, education, enrollment employment status, enrollment drinking status, and enrollment smoking status. Restricted to participants with normal visual acuity (better than 20/50). Mean difference, difference in mean scores between high and low exposure groups; *p*-value for difference in means between high and low exposure groups; positive values indicate worse performance in high-exposure groups. Range, spatial frequency (cycles/degree). Q4, fourth quartile; Q1–Q3, first through third quartile. Top 10%, blood concentrations exceeding 90th percentile. Ambient styrene exposure is 2011 National Air Toxics Assessment (NATA) estimates of annual average concentrations ($\mu g/m^3$) at the census-tract level. Blood styrene concentration (ng/mL).

For comparison, in the same models used to evaluate styrene exposure and vibrotactile threshold, a 10-y increase in age was associated with a −0.49 log microns (95% CI: −0.57, −0.41) and a −0.51 log microns (95% CI: −0.54, −0.48) decrease in vibrotactile threshold among CBS participants ($n = 307$) and the ambient study population ($n = 2{,}888$), respectively.

Ambient styrene exposure ($n = 2{,}855$) was associated with decreased standing steadiness, with statistically significantly worse stability at each quartile of exposure in comparison with the lowest quartile (Figure 3, Table S3). The linear trend across quartiles of exposure was significant when participants' eyes were closed (p-trend = 0.02), as well as open (p-trend <0.0001). The highest quartile of exposure was associated with differences in sway speed of 4.5 mm/s for both tests (βa_{Q4vsQ1} eyes closed and open). For comparison, a 10-y difference in age was associated with differences in sway speed of 7.4 (95% CI: 6.4, 8.3) and 4.4 (95% CI: 3.8, 4.9) mm/s for eyes closed and open, respectively. Expressed alternatively, ambient exposure-related associations were equivalent to differences of 0.13 and 0.24 standard deviations of mean sway speed for eyes closed and open, respectively. In contrast, we did not detect associations in blood styrene exposure analyses ($n = 299$).

Styrene exposure was also positively associated with impairments in single leg stance (Table S3). Participants in the highest quartile of ambient styrene exposure were 42% more likely to experience loss of balance during the test in comparison with the participants in the lowest quartile ($PRa_{Q4vsQ1} = 1.42$; 95% CI: 1.17, 1.71), and those with blood measurements above the 90th percentile were twice as likely to lose their balance in comparison with all others ($PRb_{P90} = 2.07$; 95% CI: 1.18, 3.61).

Unexpectedly, handgrip strength improved with increasing ambient styrene exposure ($n = 2{,}930$), demonstrating a significant linear trend (p-trend <0.0001). Higher exposure groups (i.e., the third and fourth quartile in comparison with the first quartile) were associated with increases of approximately six pounds of force (Table S3, Figure S1). We did not observe associations between blood styrene exposure and handgrip strength ($n = 310$). Handgrip strength results were robust to additional adjustment for weight (Table S4).

Overall, patterns of effect measure modification were not obvious (Tables S5–S10). We did not observe any heterogeneity of associations by sex for any of the end points (Table S5). Although results were generally similar between white and black participants, associations were stronger among those classified as "other" for grip strength ($\beta a_{Q4vsQ1} = 24.9$; 95% CI: 13.8, 35.9 vs. 4.6; 95% CI: −0.6, 9.9 and 1.2; 95% CI: −6.1, 8.4, respectively, p-interaction = 0.01) and single leg stance ($PR_{aQ4vsQ1} = 2.2$; 95% CI: 1.2, 4.0 vs. 1.2; 95% CI: 0.9, 1.6 and 1.3; 95% CI: 0.9, 2.0, respectively, p-interaction = 0.04) (Table S6). Impairments in standing steadiness were more pronounced in participants older than age 45 for the highest exposure group ($\beta a_{Q4vsQ1} = -7.0$; 95% CI: −10.8, −3.2) in comparison with younger participants

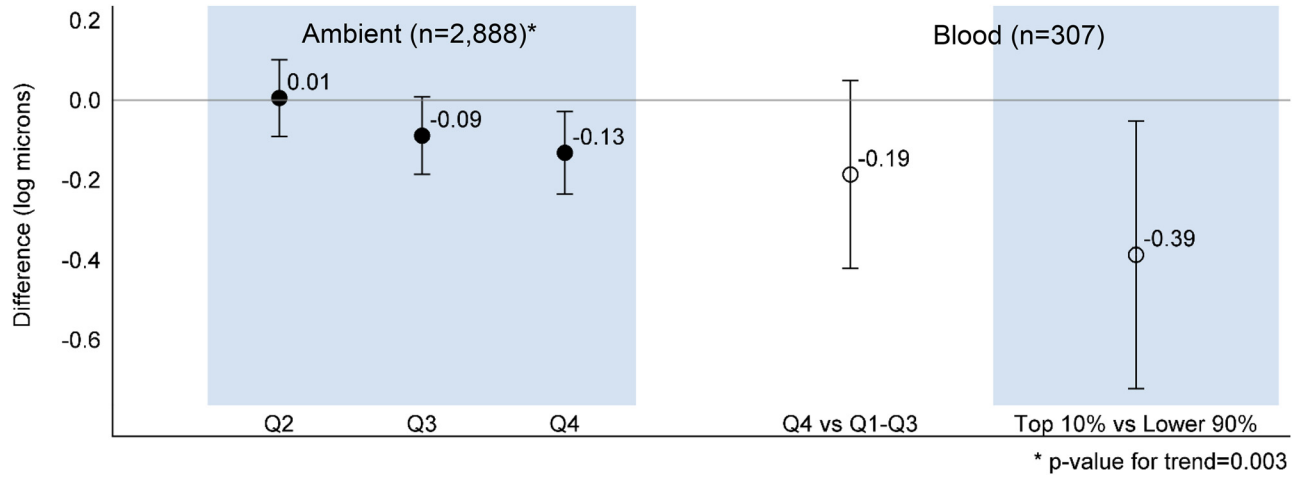

Figure 2. Ambient ($n = 2{,}888$) and blood ($n = 307$) styrene concentrations and differences in vibrotactile threshold. Note: Symbol markers and labels indicate change in vibrotactile threshold multiplied by −1 (log microns); negative values reflect sensory deficits; error bars indicate 95% confidence intervals (CI). Models adjusted for gender, age, height, race, education, enrollment employment status, enrollment drinking status, and enrollment smoking status. Ambient styrene exposure is 2011 National Air Toxics Assessment (NATA) estimates of annual average concentrations ($\mu g/m^3$) at the census-tract level. Q1, first quartile (referent exposure group); Q2, second quartile; Q3, third quartile; Q4, fourth quartile. Blood styrene concentration (ng/mL): Top 10% vs. Lower 90%, compares measurements in the highest decile to the rest of the distribution; Q4 vs. Q1–Q3, compares measurements in the highest quartile to the rest of the distribution. Numeric data provided in Table S3.

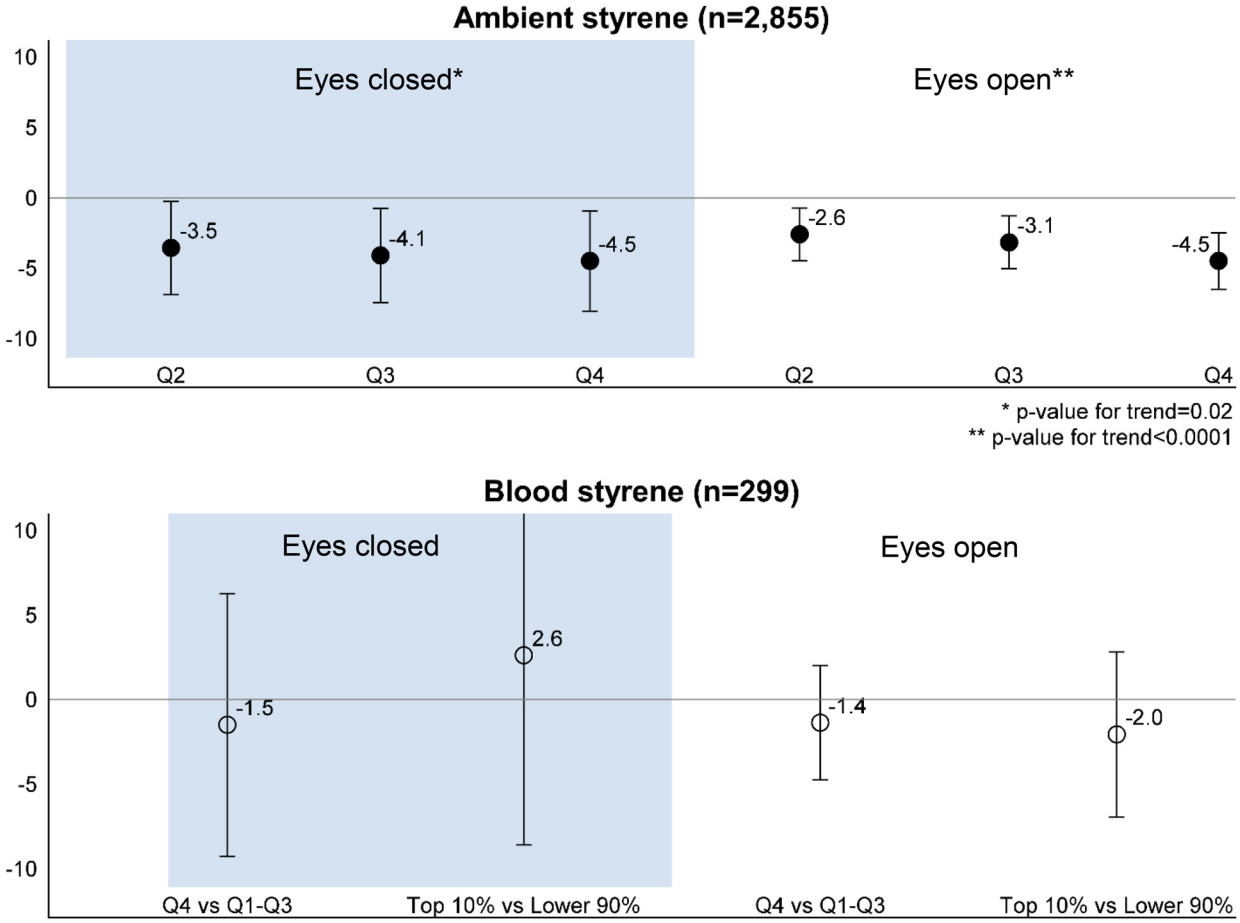

Figure 3. Ambient ($n = 2{,}855$) and blood ($n = 299$) styrene concentrations and differences in standing steadiness. Symbol markers and labels indicate change in sway speed (mm/s) multiplied by −1; negative values reflect sensory deficits; error bars indicate 95% confidence intervals (CI). Models adjusted for gender, age, race, education, enrollment employment status, enrollment drinking status, and enrollment smoking status. Ambient styrene exposure is 2011 National Air Toxics Assessment (NATA) estimates of annual average concentrations ($\mu g/m^3$) at the census-tract level. Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile. Blood styrene concentration (ng/mL): Top 10% vs. Lower 90%, compares measurements in the highest decile to the rest of the distribution; Q4 vs. Q1-Q3, compares measurements in the highest quartile to the rest of the distribution. Numeric data provided in Table S3.

($\beta a_{Q4vsQ1} = -1.9$; 95% CI: −3.5, −0.2), but age-associated differences did not persist for the third quartile of ambient styrene (p-interaction = 0.08) (Table S7). Associations between the highest quartile of ambient styrene and single leg stance were stronger in the unemployed ($PRa_{Q4vsQ1} = 1.6$; 95% CI: 1.2, 2.0) than in employed participants ($PRa_{Q4vsQ1} = 1.2$; 95% CI: 0.9, 1.7) (p-interaction = 0.05) (Table S8). Point estimates for single leg stance were higher in the rural ($PRa_{Q4vsQ1} = 1.9$; 95% CI: 1.4, 2.7) than in the urban participants ($PRa_{Q4vsQ1} = 1.2$; 95% CI: 0.9, 1.6) population (p-interaction = 0.01), but there was no evidence of heterogeneity by urban or rural location for other tests of balance (standing steadiness, p-interaction = 0.54) (Table S9). Adjustment for participation in *Deepwater Horizon* oil-spill response or cleanup did not change results (Tables S11 and S12).

Discussion

Our study of styrene-associated neurotoxicity investigated environmental exposure levels in relation to five measures of sensory and motor function. We observed styrene-associated impairment in visual sensitivity, sensory acuity, and postural function, though we did not detect evidence of impaired voluntary motor system performance. Differences in sensory performance were generally more consistent in relation to ambient styrene exposure, but we also observed associations with measured blood styrene concentration. Taken together, stratified analyses did not reveal patterns of heterogeneity in associations between styrene exposure and sensory or motor function.

When comparing mean visual contrast sensitivity scores between exposure groups across spatial frequencies, we observed modest associations, some of which achieved statistical significance. Overall, however, a consistent pattern emerged, revealing decrements in visual contrast sensitivity associated with higher ambient and blood styrene concentration. Some investigations of occupational styrene exposure among fiberglass plastic workers have also reported diminished contrast sensitivity (Campagna et al. 1995; Castillo et al. 2001), although others found no exposure-related effects (Mergler et al. 1996; Seeber et al. 2009b). Occupational exposure to organic solvents, generally, has been shown to affect visual contrast sensitivity (Costa et al. 2012), but the occupational styrene literature has emphasized loss of color vision specifically (Campagna et al. 1996; Castillo et al. 2001; Gobba et al. 1991; Iregren et al. 2005; Kishi et al. 2001).

We observed impairments in vibrotactile threshold associated with blood styrene concentration, as well as a significant monotonic exposure–response trend across increasing quartiles of ambient styrene exposure. For both exposure types, significant associations were observed among participants in the highest exposure groups (i.e., for blood styrene, the top 10% in comparison with all others, and in ambient styrene, the highest quartile in comparison with the lowest quartile). For comparison, the estimated decrement in

vibrotactile threshold associated with a 10-y age difference was greater than styrene-associated decrements, although the magnitude was comparable between a decade of aging and the highest decile of blood styrene exposure. As such, our results provide evidence of styrene-associated decreases in somatosensory function.

Measurement of cutaneous vibrotactile threshold is an established, sensitive, and well-validated test of peripheral neurologic performance in a variety of settings (Gerr and Letz 1993). Cutaneous vibrotactile threshold testing assesses the integrity of the entire somatosensory pathway from cutaneous receptor to somatosensory cortex, including the peripheral sensory nerves. Cutaneous vibratory stimuli are carried on large, heavily myelinated, sensory nerve fibers, which are believed to be more susceptible than small myelinated and unmyelinated fibers are to both systemic and focal insult. Furthermore, longer nerve fibers such as those innervating the toe are more susceptible to physiological insult than are shorter fibers innervating more proximal anatomical sites.Although this specific end point has not been widely evaluated in the styrene literature, some studies of workers exposed to styrene have found exposure-related adverse peripheral neurological effects when assessed with vibrotactile thresholds (Sato et al. 2009) as well as conventional electrophysiological testing of peripheral nerve conduction parameters (Murata et al. 1991; Yuasa et al. 1996). The literature is inconsistent, however, with other studies failing to observe associations between styrene exposure and electrophysiological outcomes (Triebig et al. 1985). The literature does not provide evidence for a specific histopathological or pathophysiological mechanism for possible effects of styrene on neurological tissues. Finally, we are not aware of studies of neurological effects of styrene at nonoccupational exposure levels similar to the range of levels reported in this study.

Handgrip strength provides information about the functional integrity of the voluntary motor system from the motor cortex to peripheral skeletal muscles. Subchronic styrene exposure induced impaired motor function in rats (Chakrabarti 2000; Terre'Blanche et al. 2011), but we are not aware of such effects in humans. We observed a paradoxical association between ambient styrene exposure and grip strength, with increased styrene concentration associated with increased grip strength, whereas we observed no associations between blood styrene concentration and grip strength. We attribute these paradoxical findings, in part, to high population variance of this measure. Detecting associations in the presence of such variance would require a strong exposure effect on the nerves being tested. Because longer nerves are typically more susceptible than shorter nerves are to toxic exposures, associations in the expected direction might have been observed had we been able to measure motor strength of the lower extremities. Unfortunately, such testing was not feasible in the current study. Tests of great-toe vibrotactile threshold and standing stability do assess the longest peripheral nerves and are likely more sensitive to subtle adverse effects. We attempted to account for some grip strength variance by adjusting for body mass index and physical activity, as well as by excluding women; however, results were unchanged in these analyses. Another possible explanation for the paradoxical association is residual confounding by socioeconomic status. In our study, ambient exposure was estimated geographically and potentially covaries with socioeconomic status. Indeed, a recent analysis of NATA 2011 data reported that census tracts with greater proportions of nonwhite and low-income populations are exposed to higher concentrations of ambient air toxics than their wealthier, less diverse counterparts are exposed to (Huang et al. 2017). In addition to potentially experiencing higher exposures, people living in communities characterized by lower socioeconomic status may also be more likely to engage in labor-intensive jobs or activities and therefore may be stronger as a consequence of occupational physical conditioning. As such, associations between ambient styrene and handgrip strength may be confounded by social factors, or simply reflect muscular training effects, as opposed to effects on motor control systems. The lack of demonstrated styrene-associated impairments in motor function at occupational levels, combined with these paradoxical results, suggest that the test of grip strength may have been capturing a phenomenon distinct from exposure-related neurotoxicity.

Tests of balance assess the integrated function of several components of the nervous system, including the vestibular apparatus, cerebellum, and proprioceptive system (Gerr et al. 2000). Loss of functional integrity of any of these systems secondary to toxic exposure may affect postural stability. In our study, we observed significant associations between all quartiles of ambient styrene exposure and decreased standing steadiness (i.e., increased sway), with a monotonic exposure response. We did not, however, detect any associations between postural sway and blood styrene concentration. Results for ambient styrene and inability to maintain single leg stance were similar to those observed for postural sway. We also observed an association between inability to maintain single leg balance and the top 10% of blood styrene exposure. Combined, these results suggest a potential impairment of the motor control system necessary to balance due to environmental styrene exposure. These findings are supported by a study of reinforced plastic boat builders, which also reported impaired postural stability in association with styrene exposure (Toppila et al. 2006).

Styrene is an established neurotoxicant at occupational exposure levels. Acute exposure causes depression of the central nervous system with anesthesia-like properties at high exposure levels (ATSDR 2010; IARC 2002; Tormoehlen et al. 2014). Epidemiologic studies to date have focused on highly exposed workers, whose average blood levels were 10–12 times higher than those of CBS participants, and 25 times higher than the general population (Brugnone et al. 1993; Cherry and Gautrin 1990; Coggon 1994; Papaleo et al. 2011; Seeber et al. 2009a; Toppila et al. 2006; Triebig et al. 1989; Vodička et al. 1995). Occupational studies demonstrate styrene-induced neurotoxicity, evident as central and peripheral nervous system effects, from both acute and chronic inhaled exposure among highly exposed workers. Acute effects include feeling drunk and tiredness (Checkoway et al. 1992), whereas impaired vision (Gobba et al. 1995; Kishi et al. 2001), vestibular dysfunction (Toppila et al. 2006), headaches (Edling et al. 1993), delayed reaction time (Jégaden et al. 1993; Tsai and Chen 1996), impaired attention and memory (Cherry and Gautrin 1990), diminished hearing (Johnson et al. 2006) and nerve conduction velocity (Cherry and Gautrin 1990; Matikainen et al. 1993; Murata et al. 1994; Rosén et al. 1978; Stetkarova et al. 1993), and abnormal electroencephalogram results (Matikainen et al. 1993; Seppäläinen and Härkönen 1976) are likely persistent, chronic effects. These effects have been observed at lower occupational exposure levels in many (Edling et al. 1993; Flodin et al. 1989; Gobba et al. 1995; Jégaden et al. 1993; Mutti et al. 1984; Papaleo et al. 2011; Tsai and Chen 1996; Tsai et al. 1997; Viaene 2001), but not all (Rebert and Hall 1994; Triebig et al. 1989), studies.

A dopaminergic mechanism for styrene neurotoxicity remains the leading mechanistic hypothesis, although it is speculative (Costa 1996). Studies suggest that styrene exposure decreases dopamine levels and increases dopamine receptors in rodents and humans (Gagnaire et al. 2006; Jarry et al. 2002; Mutti and Smargiassi 1998). In blood samples of styrene-exposed plastics workers, prolactin levels were elevated, indicating reduced prolactin inhibition by dopamine (Luderer et al. 2004). Consistent with disturbance of the dopaminergic functions of the brain,

styrene exposure potentiates a dose-dependent decrease in brain dopamine in male rats (Mutti and Smargiassi 1998), as well as cell loss and dopamine depletion in retinas isolated from female rats (Vettori et al. 2000). This finding supports the established association between occupational styrene exposure and impaired vision (Gong et al. 2002).

An important strength of the present study was the use of well-validated, quantitative measures of sensory and motor function which may detect toxicological effects earlier in disease progression than clinical assessments detect (Ferreira Ade and Baracat 2014; Gerr et al. 2000). We used a broad test battery, assessing multiple domains of sensory and motor function in a clinical research setting. Reliability of these tests (using a protocol and equipment similar to that in the present study) has been reported previously. The test–retest correlation coefficients for measurement of vibrotactile threshold of the dominant toe and nondominant toe were 0.97 and 0.91 among a convenience sample of healthy volunteers (Gerr and Letz 1988). Further, strong associations were observed between vibrotactile threshold measurements and a clinician's blinded ratings of vibration perception among a sample of patients referred for evaluation of peripheral nerve disease. A correlation coefficient of 0.68 was observed between vibrotactile threshold of the toe and a standard electrophysiological measure of the tibial nerve. In this study sample, at an assigned specificity of 90%, the sensitivity of the vibrotactile threshold for identifying distal axonopathy was 86% (Gerr et al. 1991). Test–retest correlation coefficients for sway speed among healthy volunteers were 0.92 and 0.96 for trials with eyes open and closed, respectively (Letz 1995). Test–retest correlation coefficients for handgrip strength dynamometry ranged between 0.94 and 0.97 (excluding persons with known neurological impairment), and were slightly lower (0.90) among those with known neurological impairment (Peolsson et al. 2001). For visual contrast sensitivity, the test–retest correlation coefficient was 0.87 among a small sample of healthy persons tested on several occasions (Hohberger et al. 2007). We collected these quantitative measures of neurological health outcomes from among over 3,000 participants, providing sufficient statistical power to detect small differences in sensory and motor function relevant to the observed ambient exposure range. GuLF STUDY participants arise from an understudied, diverse population (Goldstein et al. 2011), for whom we had detailed exposure and outcome information.

Associations were not entirely consistent between blood and ambient exposure metrics, which may be attributable to the unique limitations of biomarkers and proxy exposures, or the temporal windows they reflect. Biomarkers of exposure potentially introduce confounding bias, whereas ambient proxy estimates may be subject to measurement error and exposure misclassification (Weisskopf and Webster 2017). Our study attempted to address this tradeoff by assessing both types of exposure metrics. We used NATA estimates to represent typical long-term environmental exposure, and blood styrene measurements to capture internal exposure burdens resulting from recent exposures. NATA estimates have previously been used as indicators of air pollution exposure in epidemiologic studies of autism spectrum disorder (Kalkbrenner et al. 2010; Roberts et al. 2013; Talbott et al. 2015) and neurodegenerative diseases (Malek et al. 2015). Blood styrene is a validated biomarker specific to styrene exposure (CDC 2013) and it has been used extensively in occupational research (IARC 2002), as well as in general population monitoring (ATSDR 2010).

In the Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study, blood styrene demonstrated stronger correlation with indoor than with outdoor air concentrations, but outdoor sources explained more variability in levels than did indoor sources (Batterman et al. 2014; Su et al. 2013). Indeed, we observed a lack of concordance between measured blood styrene and NATA estimated annual average concentrations. At low occupational styrene levels measured in air, blood, and urine, blood demonstrated the highest correlations with recent ambient exposures (Ong et al. 1994).

The main limitations of our study revolved around temporal factors related to study design and data collection. Our study was limited by the cross-sectional design, and subsequent inability to establish temporality between styrene exposure and sensory and motor performance, though results are unlikely to have been subjected to substantial error by the limitations of cross-sectional study design. Additionally, we obtained only a single blood measurement for each individual, whereas repeated measures would potentially improve estimation of usual exposure. Samples for blood styrene concentrations were obtained 2 to 4 y prior to neurologic testing, and estimated ambient styrene exposure was assigned using residential address at enrollment (1 to 5 y before neurologic testing), the timing of which aligns with the most recent available NATA data. The timing of exposure ascertainment for both styrene metrics may introduce misclassification, depending on the relevant timing of exposure. Further, we did not account for duration of residence at the enrollment address that was used to assign ambient exposure.

Covariate information was obtained at enrollment or the time of the blood draw and may not be reflective of immediate confounding exposures near the time of the neurologic testing. As such, the possibility that potential confounders changed between exposure and outcome ascertainment may have introduced residual confounding. Another possible source of residual confounding is the crude categorization of employment, which is intended to account for confounding by socioeconomic status and general health status (being healthy enough to work), but not necessarily to provide insight into specific work-related exposures. We previously examined detailed work-related information in this population to identify possible occupational styrene exposure opportunities but ultimately found those to be negligible (Werder et al. 2018). Unemployed participants were similar to the overall population with respect to age and gender. We acknowledge the heterogeneity in this crude categorization of employment, recognizing that it is not a perfect measure of socioeconomic or health status. We believe, however, that it is a useful indicator among these individuals who were available to complete training for *Deepwater Horizon* oil-spill response efforts. Further, simultaneous adjustment for employment and educational attainment likely ameliorates confounding by social factors in this unique population.

Using an annual average ambient concentration limits interpretation. However, as routine monitoring of ambient styrene in the United States does not provide sufficient temporal or spatial coverage to support exposure interpolation methods (Li and Heap 2011; Whitworth et al. 2011; Wong et al. 2004), NATA remains the only spatially referenced exposure data source with sufficient geographic coverage for our study region. Although the assumptions inherent to an annual average estimate of air pollution potentially limit interpretation, NATA data are a valid estimation of usual exposure levels experienced by Gulf region residents. Long-term blood and ambient styrene trends indicate that year-to-year regional variation in concentration is generally not substantial, suggesting that an annual average estimate is an appropriate assessment of exposure (Ashley et al. 1994; CDC 2013; Churchill et al. 2001; Cohen et al. 2002). If long-term styrene exposure exerts chronic sensory or motor effects, NATA estimates may be a more relevant exposure metric than measures with more precise temporal windows.

Although styrene-associated impairment of sensory and motor function was not universally apparent across all exposure and

outcome measures, in aggregate, our results are suggestive of a neurotoxic effect of styrene. The standing steadiness and vibrotactile threshold tests are well-established and validated measures of neurologic performance with known standard covariates (Ferreira Ade and Baracat 2014; Gerr and Letz 1994a, 1994b). Testing sensory function in this way may allow for early detection of subclinical neurotoxicity among groups exposed at levels relevant to the general population. Furthermore, large fiber function abnormality may be an early indicator of neurological disease. Future research is needed to confirm these findings and to determine whether styrene-induced neurotoxicity derived from environmental exposures persists over time, and how it may relate to future risk of clinically apparent neurological disease.

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